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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/647,789	08/25/2003	Daniel P. Wermeling	INT-001 B	2016

51414 7590 04/16/2009

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EXAMINER	
BETTON, TIMOTHY E	
ART UNIT	**PAPER NUMBER**
1617	

NOTIFICATION DATE	DELIVERY MODE
04/16/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/647,789	WERMELING, DANIEL P.	
	Examiner	Art Unit	
	TIMOTHY E. BETTON	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 January 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8,10-13,16-20 and 46-72* is/are pending in the application.

4a) Of the above claim(s) *1-8,10-13,16-20 and 46-52* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *53-72* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' Remarks filed on 29 January 2009 have been acknowledged and duly made of record.

Telephonic Interview

In the telephonic interview of January 22, 2009, the Attorney Davis elucidated aspects with regard to the inventive objective of the claimed invention. In addition, the Attorney was asked to provide evidence that the internal configuration of the intranasal unit-dose delivery device was distinct from the same class of devices that are already in commercial use. Accordingly, the Attorney was further requested to provide the distinction in view of the common practice in the art to optimize characterization of the spray plumb, i.e., adjustable mechanism to achieve the plume of claimed invention.

Response to Arguments

Applicants aver the *Rejection of Claims 53-59, 62-67, 70, and 71 Under 35 U.S.C. § 103(a)*on the grounds that the Ward-Smith reference, principally, does not teach sufficient information to identify the spray pumps of claimed invention.

Further, applicants' disclose:

As discussed during the telephone interview on January 22, 2009, spray plume geometry is an important feature that impacts how quickly and how much of the therapeutic agent is absorbed through the nasal mucosa following intranasal administration using a unit-dose delivery device. ***Also, spray plumes can have widely different features, e.g., differences in the droplet size at specific distances from the end of the spray nozzle, and***

differences in the width (i.e., the span) of the spray plume as it advances from the end of the spray nozzle. Each of these features have a profound effect on the pharmacokinetics of drug delivery.

Further, applicants' disclose:

[…]. Applicant respectfully submits that the skilled artisan, based on the teachings of the applied references, would have had no reason whatsoever to believe that using a spray plume with such features could provide unexpectedly higher butorphanol concentrations in the blood plasma relative to the prior art, multi-dose device. Indeed, none of Weinstein, Levin, or Ward-Smith provide any suggestion to select, for intranasal delivery of an opioid, a spray plume having a "Dvl0 of from about 14.3 gm to about 17.1 gm and a Dv50 of from about 31.0 gm to about 35.3 gm" from the multitude of potential spray plumes.

Applicants' arguments are considered but are not found persuasive because in the well-known art of pharmacokinetics, it would well be within the purview of the one of skill to engineer and/or manipulate the configuration of the device in such a way as to achieve the desired spray plume.

Further, it is not clearly understood with regard to the current amendments to the claims what is the inventive objective in view of the specification being absent of any evidence that such amendments distinguish the said invention in the Examples as disclosed.

Applicants' further disclose:

Applicant has discovered that the particular plume geometry claimed has an important and beneficial effect on the intranasal administration of an opioid containing composition. In particular, as illustrated in Figure 1 of the application, ***this particular spray plume provides an unexpectedly higher butorphanol concentration in the blood plasma relative to the prior art, multi-dose device. Applicant respectfully submits that the skilled artisan, based on the teachings of the applied references, would have had no reason whatsoever to believe that using a spray plume with such features could provide unexpectedly higher butorphanol concentrations in the blood plasma relative to the prior art, multi-dose device.*** *Indeed, none of Weinstein, Levin, or Ward-Smith provide any suggestion to select, for intranasal delivery of an opioid, a spray plume having a "Dvl0 of from about 14.3 gm to about 17.1 gm and a Dv50 of from about 31.0 gm to about 35.3 gm" from the multitude of potential spray plumes.*

Accordingly, applicants' arguments are considered but are not found persuasive, because it would have clearly been obvious to try variable spray plumes for optimal therapeutic effect, i.e, increased surface area of the active agent to the intranasal passages.

These unexpected results are no where elucidated in the current specification. Support or suggestion drawn to unexpected results is not evident from the working models or Examples. The current amendments in the claims are not disclosed in the specification in such a way as to distinguish the claimed invention based upon unexpected results.

Examiner contends that in the absence of any disclosure drawn specifically to clearly show the delineation, applicants' unexpected results could be readily achievable via due experimentation into the engineering and specific configuration of intranasal devices already commercially marketed.

The Examiner further contends that applicants disclosure that the manufacturer, model, or design parameter of the spray pumps are absent in any of the references employed in the current rejection is irrelevant.

The instant claims do not contain such limitations. The design parameter, however, was discussed extensively during the said interview and evidence currently has not been provided to satisfy the request of the Examiner as to what makes this claimed configuration distinct and different in order to have such alleged unexpected results (in light of devices on the market which clearly make obvious the claimed invention based upon adjustable spray plumes).

Further, applicants aver the *Rejection of Claims 60, 61 and 72 Under 35 U.S.C. § 103(a).*

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, there is clear and precise teaching, suggestion, and motivation to combine based upon each and every element of the instant invention being taught or encompassed by obvious subject matter.

The knowledge of one of skill is inclined to regard the art of pharmacokinetics and the need to produce more therapeutically sound nasal dosage forms via the well-known art of increasing the surface area of intranasal active agent particulate.

For the reasons already made of record, the rejections of 29 July 2008 are maintained.

Status of the Claims

Claims 1-8, 10-13, 16-20, 46-52 have been withdrawn. Claims 9, 14-15, 21-45, and 68-69 are cancelled. Claims 53-67 and 70-72 are pending for further examination on the merits.

Claim Rejections- 35 U.S.C. 103(a)

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

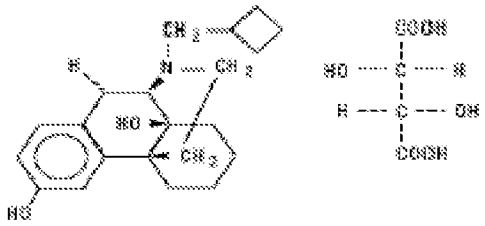
> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 53-59 and 62-67, 70, and 71 are rejected under 35 U.S.C. 103(a) as being unpatentable over Weinstein et al. (USPN 5437267) and Levin, B. (PGPUB US 2001/0004644 A1) in view of Ward-Smith, S., (Semi-automated testing of nasal sprays. (Nasal Spray Testing, Pharmaceutical Technology Europe, (2002), pages 1-9).

For evidentiary purposes, applicant discloses butorphanol tartrate in instant claims 54 and 71 which has an intranasal delivery formulation device system called Stadol NS®, Bristol-Myers Squibb in 1991 was approved by the FDA for marketing as a prescription medication (A Brief History of Bristol-Myers Squibb, 2007, Newsroom, page 3, 8th paragraph).

Additionally for evidentiary purposes:

Butorphanol tartrate is a synthetically derived opioid agonist-antagonist analgesic of the phenanthrene series. The chemical name is (-)-17-(cyclobutylmethyl) morphinan- 3, 14- diol [S-(R*, R*)] - 2,3 - dihydroxybutanedioate (1: 1) (salt). The molecular formula is C21H29 NO2, C4H6O6, which corresponds to a molecular weight of 477.55 and the following structural formula:



Butorphanol tartrate is a white crystalline substance. The dose is expressed as the tartrate salt. One milligram of the salt is equivalent to 0.68 mg of the free base. The n-octanol/aqueous buffer partition coefficient of butorphanol is 180:1 at pH 7.5.

STADOL NS (butorphanol tartrate) is an aqueous solution of butorphanol tartrate for administration as a metered spray to the nasal mucosa. Each bottle of STADOL NS contains 2.5 mL of a 10-mg/mL solution of butorphanol tartrate with sodium chloride, citric acid, and benzethonium chloride in purified water with sodium hydroxide and/or hydrochloric acid added to adjust the pH to 5.0. The pump reservoir must be fully primed (see PATIENT INSTRUCTIONS in HOW SUPPLIED) prior to initial use. After initial priming each metered spray delivers an average of 1.0 mg of butorphanol tartrate and the 2.5 mL bottle will deliver an average of 14–15 doses of STADOL NS. If not used for 48 hours or longer, the unit must be reprimed (see PATIENT INSTRUCTIONS in HOW SUPPLIED). With intermittent use requiring repriming before each dose, the 2.5 mL bottle will deliver an average of 8–10 doses of STADOL NS depending on how much repriming is necessary. (RXLIST monograghs; The Internet Drug Index, (2007), Butorphanol Tartrate; Description, pages 1 and 2). Above reference discloses general specifications which are obvious over the subject matter in applicant's

invention in that an opioid intranasal delivery device is taught with ingredients that are not identical but contain similar constituents as disclosed in instant claims.

Weinstein et al. teach a device for the intranasal delivery of a medicament regimen to the nasal membranes for the treatment of such conditions as rhinitis (Abstract). Referenced Figure 1A depicts a perspective view of another embodiment of invention including 2 (in comparison to 1 or more claimed in instant claim 53) medicament canisters/chambers. The term chamber is interchangeable with the term vessel of instant claim 53. All other depictions for Figures 2 through Figure 7 incorporate the use of more than two medicament canisters with variations in configuration thereof for optimal therapeutic delivery (Drawing sheets 1-3, columns 3-8).

Weinstein et al. does not teach use of an opioid formulation in referenced device. Additionally, Weinstein et al. does not teach a description of spray plume actuation or volume median measurements in terms of Dv parameters.

Levin teaches the practicing methods comprising intranasally administering to the patient a pharmaceutical composition comprising a local anesthetic. Levin further discloses butorphanol tartrate for use in intranasal device for muscular headaches (page 2, section [0018]; page 21, section [0200]; page 39, claim 24).

However, Levin, too, does not teach a description of spray plume actuation or volume median measurements in terms of Dv parameters.

However, Ward-Smith, which teaches nasal spray formulations consist[ing] of the drug suspended or dissolved in an aqueous medium, which is filled into a bottle with a metered spray pump. Pump actuation by the patient delivers the drug in fine droplets into the nasal cavity. The pump is an integral part of the whole assembly and plays a crucial role in delivering an accurate

dose to the correct absorption site. Of particular importance is the droplet size distribution produced by the pump, which must be optimized to increase nasal deposition and minimize lung deposition or absorption in the gastrointestinal tract (page 1, 1st paragraph). Further, Ward-Smith encompasses the spray droplet size ranges disclosed by instant claims with a description of the Spraytec with Nasal spray Actuator with a 200mm Fourier lens, [which] is [...] most typically used in this application, allowing measurements in the 1-400 [micro]m size range.

Further, Ward-Smith teaches the measurements at three different distances between the laser diffraction measurement zone and the tip of the pump (measurements of 3,6, and 9 cm) (page 3, Experimental, 4th sentence). Independent claim 53 and dependent claims 62-70 discloses a positioning of the device 1 cm and 5 cm away, respectively from a laser detection pathway. Ward-Smith teaches nasal spray formulations consist[ing] of a drug suspended or dissolved in an aqueous medium same as disclosed in instant claim 58. Laser diffraction as a technique for particle sizing is taught (page 2 and 3, Droplet sizing using laser diffraction). Multiple measurements are required for each measurement point to assess the measurement precision. The 10th, 50th and 90th percentiles (Dv10, Dv50 and Dv90) must be reported for the size distributions measured during each stage. The span of the size distribution must also be reported (Span = [Dv90 - Dv10/Dv50]) according to Ward-Smith et al. (pg 3, Experimental, 5th sentence). Instant claims 63 and 64 are obvious in view of Ward-Smith. Referenced page 6-8 teaches actual result data obtained for manual actuation pumps and as a function of pressure (semi-automated) pumps. The reference discloses ranges higher in comparison to instant claimed ranges with the exception of some examples of conclusive data. One of ordinary skill in the pertinent art would at once recognize the necessity to properly adjust the ranges.

It, therefore, would be prima facie obvious to modify the device and medicament administered in Weinstein et al. to an opioid. Accordingly, it would be obvious to modify the device of Levin, which does teach a practicing administration of butorphanol tartrate in an intranasal device. The motivation to combine would be obvious based in view of Ward-Smith, which does teach the specific parameters of efficacious administration, i.e., description of spray plume actuation, the detection of droplet size distribution, specific droplet size, etc.

Claims 60, 61 and 72 are rejected under 35 U.S.C. 103(a) as being unpatentable over Weinstein et al. (USPN 5437267) and Levin, B. (PGPUB US 2001/0004644 A1) in view of Ward-Smith, S. as applied to claim 53-59 and 62-67, 70, and 71 above, and further in view of Illum et al. (Intranasal Delivery of Morphine, The Journal of Pharmacology and Experimental Therapeutics, 2001,vol.301, no.1, pages 391-400), Pezron et al. (Prodrug strategies in nasal drug delivery, Expert Opin. Ther. Patents (2002) 12(3): 331-340), and Manjushree et al. (Intranasal fentanyl provides adequate postoperative analgesia in pediatric patients, CAN J ANESTH 2001, 49:2, pages 190-193) in view of Midha et al. (USPN 6127385).

Illum et al. teach the intranasal delivery of morphine, a potent narcotic analgesic, [which] produces a variety of pharmacological responses by interacting with the opioid receptors in the nervous system (page 391, 1st paragraph). Further, Illum et al. teach butorphanol as a practicing analgesic agent that can be effectively and rapidly absorbed from the nasal cavity (page 391, 3rd paragraph). Additionally, Illum et al. teach a pH range of 4.02 and 3.81, respectively which are specific to the broad pH range (pH of about 3 to about 6) disclosed in instant independent claim 53 (page 392, Formulation Preparation, 2nd and 3rd paragraph).

Illum et al. does not teach the intranasal opioid formulation with citrate buffered water or a sweetener. Illum et al. teach said formulation with an absorption-promoting agent such as chitosan.

Pezron et al. teach strategies for enhanced nasal drug delivery via taste modification of these bitter moieties by use with moieties that lack bitterness (page 337, Miscellaneous applications, 2nd paragraph).

Pezron et al. does not teach nasal drug formulation with a sweetener to mask the bitter taste due to administration.

Manjushree et al. teach the well-established use of the intranasal opioid fentanyl with the nasal carrier citrate in the formulation (page 191). Further, Manjushree et al. teach the scope of prolonged use of fentanyl citrate without any adverse effects.

Manjushree et al. does not teach an intranasal opioid with a sweetener or flavoring agent.

However, the Examiner refers to Midha et al., which teach an embodiment of a nasal formulation containing [active agent] dissolved in aqueous or non-aqueous solvent, an antioxidant and aromatic oils as flavoring agents (column 4, lines 59 to 63). In instant claim 61, aromatic oils are disclosed as rosemary oil, spearmint oil, thyme oil, etc. Instant claim 72 specifically discloses sucrose, but Midha et al. does not teach sucrose. However, it would have been obvious to interchange flavoring agents based on the list disclosed within instant claim 61.

Further, in view of the limitations drawn specifically to *one or more sealed vessels containing a sterilized, preservative -free pharmaceutical composition*, the MPEP cites thus:

Omission of an Element and Its Function Is Obvious if the Function of the Element Is Not Desired

Ex parte Wu , 10 USPQ 2031 (Bd. Pat. App. & Inter. 1989) (Claims at issue were directed to a method for inhibiting corrosion on metal surfaces using a composition consisting of epoxy resin, petroleum sulfonate, and hydrocarbon diluent. The claims were rejected over a primary reference which disclosed an anticorrosion composition of epoxy resin, hydrocarbon diluent, and polybasic acid salts wherein said salts were taught to be beneficial when employed in a freshwater environment, in view of secondary references which clearly suggested the addition of petroleum sulfonate to corrosion inhibiting compositions. The Board affirmed the rejection, holding that it would have been obvious to omit the polybasic acid salts of the primary reference where the function attributed to such salt is not desired or required, such as in compositions for providing corrosion resistance in environments which do not encounter fresh water.). See also In re Larson, 340 F.2d 965, 144 USPQ 347 (CCPA 1965) (Omission of additional framework and axle which served to increase the cargo carrying capacity of prior art mobile fluid carrying unit would have been obvious if this feature was not desired.); and In re Kuhle, 526 F.2d 553, 188 USPQ 7 (CCPA 1975) (deleting a prior art switch member and thereby eliminating its function was an obvious expedient).

B. Omission of an Element with Retention of the Element's Function Is an Indicia of Unobviousness

Note that the omission of an element and retention of its function is an indicia of unobviousness. In re Edge, 359 F.2d 896, 149 USPQ 556 (CCPA 1966) (Claims at

issue were directed to a printed sheet having a thin layer of erasable metal bonded directly to the sheet wherein said thin layer obscured the original print until removal by erasure. The prior art disclosed a similar printed sheet which further comprised an intermediate transparent and erasure-proof protecting layer which prevented erasure of the printing when the top layer was erased. The claims were found unobvious over the prior art because the although the transparent layer of the prior art was eliminated, the function of the transparent layer was retained since appellant's metal layer could be erased without erasing the printed indicia.).

Thus, it would be *prima facie* obvious to the one of skill at the time of the invention to recognize a reasonable expectation of success via the combining and incorporating together of the teachings, methods and modification of Weinstein, Levin, and Ward-Smith, principally. Weinstein teaches embodiments drawn to variable intranasal devices, which adequately encompasses the device as claimed of current invention. The deficiency in Weinstein is resolved by Levin, which teaches the practicing methods comprising the intranasal administration of the bioactive agent butorphanol tartrate. Ward-Smith further cures the deficiency of Levin by teaching the mechanics behind the optimal spray plumb for increased therapeutic efficacy into the nasal passages. The common measurement referred to as Dv's are adequately elucidated in the reference in obviousness over the claimed invention.

Further, Illum, Pezron, Manjushree, and Midha teach the limitations as drawn to the present claims in reference to pH, sweeteners, nasal citrate carriers, flavoring agents, respectively. Accordingly, in addition to the references cited as in further view of the limitations of claim *one or more sealed vessels containing a sterilized, preservative -free pharmaceutical*

composition, it would be prima facie obvious to considered the variability of construction of said device which is indicated to achieve the same therapeutic end (Please refer to citations from the MPEP above).

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Timothy E. Betton whose telephone number is (571) 272-9922. The examiner can normally be reached on Monday-Friday 8:30a - 5:00p.
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197

(toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

TEB
/SREENI PADMANABHAN/

Supervisory Patent Examiner, Art Unit 1617